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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,520	07/16/2003	Adrien R. Beaudoin	850865.90015	9012

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EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,520	BEAUDOIN ET AL.	
	Examiner	Art Unit	
	Traviss C. McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892 or by applicants on form PTO-1449, they have not been considered.

It is noted that reference 32 , p. 1072 of the Sigma-Aldrich catalogue, has been lined through as there is no date available for this reference.

Claim Objections

Claim 8 is objected to because of the following informalities: the claim lacks a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **inhibiting** the activity of an NTPDase enzyme comprising contacting the enzyme to a C8 substituted purine nucleotide **which is substituted with an –O-X group, a –S-X group, or an -NH-X group**, wherein X is an alkyl group, does not reasonably provide enablement for **modulating** the enzyme with a C8 substituted purine nucleotide **which is substituted with any substituent other than H**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims without undue experimentation.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

Claim 1 is drawn to a method of modulating the activity of an NTPDase enzyme comprising exposing the enzyme to a C8 substituted purine nucleotide, wherein the purine nucleotide is substituted at the C8 position with a substituent other than H. Claim 2 provides the purine is adenine. Claim 3 provides the substituent is an ether, a thioether, or an amine. Claim 4 provides the enzyme activity is inhibited. Claim 5 provides the substituent is –O-X. Claim 6 provides X is an alkyl group. Claim 7 further defines the alkyl groups. Claim 8 provides the substituent is –S-X. Claim 9 provides X is an alkyl group. Claim 10 further defines the alkyl groups. Claim 11 provides the substituent is –NH-X. Claim 12 provides X is an alkyl group. Claim 13 further defines the alkyl groups. Claim 14 further limits the identity of the compound. Claim 15 provides the enzyme is in a biological system and the method results in a modulation of the level of various purine nucleotides/nucleosides. Claim 16 provides the enzyme is in a biological system and the method results in a modulation of the activity of a biological process in the system. Claim 17 provides the process is aggregation or thrombogenecity. It is noted that the number of possible substituents identified by the phrase "a substituent other than H" is seen to be in the millions of possible substituents and include any possible substituent, being organic moieties, inorganic moieties, vectors, proteins, peptides, amino acid sequences, and nucleic acids, to name a few.

The state of the prior art

NTPDase, nucleoside triphosphate diphosphohydrolase, is known to be a family of ectonucleotidases which catalyze the hydrolysis of β and γ-phosphate of extracellular nucleotides. These enzymes were previously known as ATPDases, ecto-ATPases, and E-type

ATPase. These enzymes are known to be present in all physiological systems where they modulate the extracellular concentrations of nucleotides, thereby controlling purinoceptor-mediated effects, via inhibition of the NTPDase enzyme (see Gendron et al., "Inhibitors of NTPDase: Key Players in the Metabolism of Extracellular Purines", Purine and Pyrimidine Metabolism in Man X, pp. 119-123, 2000).

The level of predictability in the art

Document 60 on the IDS filed 2/18/2004 states teaches of the unpredictability of the use of modified compounds in inhibiting NTPDase wherein it is stated that "from these data, it appears that both the **position and nature** of the substituents are important to confer resistance to enzyme hydrolysis". That is, the art teaches that the position of the substituent and the identity of the substituent are important in conferring their activity. Moreover, a review of the data on figure 1 shows that indeed, unpredictable results are obtained when divergent moieties are substituted in the same position (se for example the 8-Br-substituted compound and the 8-BuS-substituted compound). As such, one would not be able to predict which moieties would have a inhibiting effect on the enzyme and which would not. Moreover, the art is silent to method of increasing the activity of the enzyme with this class of compounds. All art is seen to be drawn to inhibiting the enzyme, as such, performing a method of anything but inhibiting the enzyme would require undue experimentation.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed

method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written.

The existence of working examples

The working examples set forth in the instant specification are directed to various methods of making and using only adenosine compounds which are O-alkyl, S-alkyl, or NH-alkyl substituted in the C8 position of the purine. There has not been provided sufficient evidence which would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that any compound of claim 1 would indeed provide the claimed activity.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the use of any compound of claim 1 as claimed without undue experimentation. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation. One skilled in the art would be confronted with an undue burden of experimentation to isolate and/or produce, characterize, and test the various compounds of claim 1 to determine if indeed they have efficacy as claimed. Since the number of possible compounds is seen to be in the hundreds of thousands, the examiner believes this is indeed undue experimentation. As set forth supra, applicants have successfully shown methods of inhibiting the enzyme using compounds comprising O-alkyl, S-alkyl, or NH-alkyl substituted in the C8 position of the purine.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a method which comprises "exposing" the enzyme to a nucleotide. It is unclear as to what is intended by the phrase "exposing". It is noted that exposing is not seen to require actual contact, and therefor it is unclear how the method would actually function if the 2 agents did not actually make contact. The examiner has interpreted the claim as a method comprising "contacting the enzyme with a C8 substituted purine nucleotide".

Claim 2 is indefinite wherein the claim reads "wherein the purine nucleotide is adenine". It is unclear how a nucleotide can be adenine, as adenine is known to be a non-saccharide containing base and nucleotides are known to be phosphorylated sugar-containing moieties. The purine nucleotide can **comprise** adenine, or the purine nucleotide can be adenosine, but it is unclear what applicants intend by stating the purine nucleotide is adenine.

Claims 5, 8, and 11 are indefinite as they provide that the substituent is either –O-X, -S-X, or –NH-X, however none of these claims define X. Applicants should define any variables or R-groups in the claims in which they occur.

Claim 14 is indefinite wherein the claim provides that the nucleotide is one of various compounds listed alphanumerically (i.e., compound 6a, 6b, 6c). However, it is unclear as to what compounds 6a, 6b, 6c, etc are. Applicants should not point elsewhere in their claims to that which they are claiming. Applicant's claims should contain all the information to that which they

are claiming. Applicants are encouraged to include that which they are claiming in the claims, i.e., include the actual identity of the compounds claimed using structural or nomenclatorial representation.

Claim 14 recites the limitation "compounds 7a, 7b, 7c, 7d, 7e, 8a, 8b, 8c, 8d, or 8e". There is insufficient antecedent basis for this limitation in the claim as the examiner is not able to locate any compounds represented by these identifiers anywhere in the specification or drawings.

Claim 17 is indefinite wherein the claim provides the biological process of claim 16 is aggregation **and** thrombogenecity. It is unclear how the process can be both of these conditions and as such, the examiner has interpreted this to as aggregation **or** thrombogenecity.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Gendron et al. (document 60 of IDS).

Document 60 discloses methods of inhibiting NTPDase using various adenosine derivatives which are substituted on the C8 position with –O-alkyl, -S-alkyl, and –NH-alkyl moieties (see figure 1 and table 1). Moreover, it is noted that the methods of 15-17 are seen to be inherently produced when practicing the method of claim 1. As evidenced by applicant's arguments filed on April 23, 2002, in application number 09/591,177 (which is available as art to show the state of the art at the time of the invention), applicants state that "the methods of claims 17-19 (equivalent to method claims 15-17 of the instant application) relate to subsequent downstream events which result from the modulation of NTPDase activity. Therefore, applicants respectfully submit that the methods claimed in claims 15-19 (1-17 of the instant application) are related in that they define a chain of events stemming from exposing an NTPDase to a compound of Group I of the invention. The compounds directly obtain only the process of group II (claims 1-14 of the instant application). The direct consequence of Group II modulation of NTPDase activity (claims 1-14 of the instant application) is the modulation of the level of nucleotides/nucleosides (claim 15 of the instant application), and the direct consequence of that is the induction of biological activity (claims 16-17 of the instant application)". As such, per the art recognized normal chains of events, a method which meets the limitations of claim 1 would inherently meet the limitations of claims 15-17.

Claims 1-4, 8-10, and 15-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Beaudoin et al. (reference 33 of IDS).

Beaudoin et al. disclose that 8-BuS-ATP is an effective NTPDase inhibitor in the micromolar range (see page 132, middle paragraph). 8-Bu-S-ATP is known to be adenosine

triphosphate substituted in the 8 position with a thio-butyl group. As set forth supra, the methods of claims 15-17 are inherently preformed when the method of claim 1 is performed.

Claims 1-4, 11-12, and 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (reference 51 of IDS).

Chen et al. disclose that 8BrATP and 8-(6-aminohexyl)amino-ATP act as ecto-ATPase inhibitors (see table 1 and 1st paragraph of results bridging pages 443-444). 8BrATP is known to be ATP substituted at the 8 position with Br and 8-(6-aminohexyl)amino-ATP is known to be ATP substituted at the 8 position with an N-linked alkyl group comprising an amino group.

The examiner would also like to make of record Hampton et al., "Species- or Isozyme-specific Enzyme Inhibitors. 4. Design of a Two-Site Inhibitor of Adenylate Kinase with Isozyme Selectivity", J Med. Chem., vol. 25, pp. 638-644, 1982, who discloses 8-SEt-ATP, which is seen to be an adenosine nucleotide comprising a thioethyl group attached to the 8 position of the base.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C. McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Traviss C. McIntosh III
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June 1, 2006

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